See corresponding article on page 343.

Can dietary flavonoids play a role in Alzheimer's disease risk prevention? Tantalizing population-based data out of Framingham

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Alzheimer's disease (AD) and related dementias (ADRD) are the cause of disability, institutionalization, and mortality worldwide. It is estimated that 46 million people are living with dementia (1), for which no treatment exists. This emphasizes the need for identification of preventive strategies. The pathophysiology of Alzheimer disease is multifactorial, and modifiable lifestyle factors, including diet, are potential targets for the development of preventive strategies.

The article authored by Shishtar et al. (2) in this issue of *The American Journal of Clinical Nutrition* examines the prospective relation between total habitual dietary flavonoid intake, as well as the 6 most commonly consumed flavonoid classes, and the risk of AD and ADRD. Currently there are limited data on the relative importance of the roles different flavonoid classes play in AD. This article provides new evidence that a higher habitual intake of several flavonoid subclasses (flavonols, anthocyanins, and flavonoid polymers) is associated with lower risk of AD.

The Framingham Offspring Cohort impressively included nearly 3000 participants with a mean age close to 60 y, and followed them with exams every 4 y for nearly 2 decades, during which time 193 ADRD events occurred. Although the number of cases was on the smaller side, their data suggest substantially lower risks (ranging from 42% to 76% lower) among participants with the highest (top 60% percentile) as opposed to the lowest intake of the 3 flavonoid subclasses: flavonols, anthocyanins, and flavonoid polymers. Although the study presents important data and strong associations, the magnitude of association was unexpectedly large and merits a bit of further speculation. The cutoffs for the top categories of anthocyanin and flavonol intakes were 16.4 and 14.2 mg/d, respectively, which are comparable with habitual intakes in other US cohorts of middle-aged and older individuals and amounts that have been associated with a 15%–32% lower risk of cardiovascular disease or type 2 diabetes mellitus (3–6). This corresponds to low habitual intakes of flavonol- and anthocyanin-rich foods: a cup of tea [8 oz (236.59 mL)]contains 9.6 mg flavonols, a medium apple 7.6 mg, whereas a half-cup of blueberries and of strawberries contains 120.8 and 20.5 mg anthocyanins, respectively (7, 8).

To understand the large effect sizes in the present study, we note that associations between risk factors and diseases of old age can be particularly difficult to address in observational epidemiology (9). Spurious associations could occur if, for instance, selection into the present study (Framingham residents free of ADRD had to attend the fifth exam, fill out an FFQ, and attend $\geq$1 following exam for the assessment of the study outcome) was associated with flavonoid intake. High mortality risk in older age presents another common problem in studies of dementia that rely on exam visits that are years apart, because a diagnosis of dementia at time of death might be missed if a participant appeared cognitively normal at the last attended study exam. Such underestimation of dementia incidence could also inflate the observed effect size (9).

Key steps going forward are of course to replicate these data in other cohorts. As also pointed out by the authors, there is a paucity of longitudinal data with repeated dietary assessments among participants followed from midlife and through older age with detailed clinical adjudication of Alzheimer events. Although even prospective studies can run a risk of reverse causation if the study population is older, where cognitive decline may already be accelerating, or if follow-up is too short, the Framingham Offspring Cohort seems particularly well-suited for this sort of analysis. The authors were able to assess flavonoid intake at exams 5 through 9 and evaluate the risk of AD/ADRD among participants free of cognitive problems at baseline even with several options for lag time between exposure and follow-up. Furthermore, a number of previous studies outlined by the authors relied on a single baseline assessment of intake or did not capture the breadth of dietary flavonoids present in the habitual diet. This study addresses many of the aforementioned issues by using repeated measurements, a validated semiquantitative FFQ, and a well-established flavonoid subclass classification (10).

What are some of the other limitations we might wish to address before recommending diets high in flavonoid-rich foods for the prevention of AD and integrating such advice into public

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health recommendations? It would have been nice to have seen some food-based analyses, suggesting that the top sources of the flavonoids of interest (berries, pears, onions, red wine, and tea) were associated with risk of AD in the expected direction. Food-based analyses are not only easier for the public to interpret but also bring to mind considerations of what a typical diet might look like for those who are the highest flavonoid consumers. Although the authors adjusted for a range of factors (age, sex, education, total energy, *APOE4* allele, smoking, physical activity, BMI, prevalent vascular disease and diabetes, omega-3 fatty acids, EPA, DHA, lutein and zeaxanthin, vitamin and mineral supplement use, alcohol, and overall diet quality assessed by the 2010 Dietary Guidelines Adherence Index), it might have been worthwhile to also address the impact of adjustment for cereal fiber or whole grains, as well as other foods such as cruciferous vegetables. An additional model, including total fruit and vegetable intake, would have been of interest to see if their addition substantially attenuated the observed relation, and may have added further weight to the specific relative importance of the flavonoids.

Dementia is a progressive disease, characterized by long-term and gradual decline in cognitive abilities and psychological changes leading to disturbances in daily function. Because the Mini Mental State Examination was part of all the exams and used to refer participants with suspected cognitive decline to a neurologist, it would have been powerful if the authors had shown that the associations were also mirrored by changes in cognitive scores. In 2012, Devore et al. (11) showed that in >16,000 US nurses, the highest, compared with the lowest, intake of anthocyanin was associated with a reduced rate in cognitive decline (global score, averaging all 6 cognitive tests = 0.03 standard units; 95% CI: −0.01, 0.06); effect estimates that are equivalent to ∼1.5–2.5 y of age in their study population.

Further validation of the growing number of promising observational studies suggesting that flavonoids, in particular anthocyanins, flavanones, flavonols, and flavan-3-ols, are associated with lower risks of chronic diseases would be greatly enhanced if validated urinary/plasma biomarkers for the metabolites of the specific flavonoids of interest were available (12–14).

Another major research gap for the field is the limited clinical trial data on cognitive decline and other risk markers for AD. This gap might be addressed soon, because the NIH has funded the MIND (Mediterranean-DASH Diet Intervention for Neurodegenerative Delay) randomized controlled trial that is designed to test the effects of a 3-y intervention of a hybrid of the Mediterranean and the Dietary Approaches to Stop Hypertension diets on cognitive decline among 600 individuals aged 65 y and older (NCT02817074). The MIND diet emphasizes berries, over other fruits, in addition to fish and green, leafy vegetables. Results are expected after the study's completion in 2022.

All in all, these data add to our understanding of the potential of flavonoids for reducing the risk of dementia. There is growing plausible mechanistic evidence for a role of specific flavonoids. After ingestion flavonoids are extensively metabolized and the determinants of interindividual variability in metabolism are a key research gap, including the role of the gut microbiome (12). Many of these metabolites can cross the blood–brain barrier with the potential to exert neuroprotective (via cerebral blood flow and blood pressure effects) and antineuroinflammatory effects (upregulating neurogenesis and neuroplasticity), with recent evidence suggesting the metabolites may also be a mediator of the microbiome–gut–brain axis (15, 16). The present study is an important addition to the growing literature on flavonoids and dementia. While we wait for the results of the MIND trial, we should recall the robust evidence-base supporting beneficial health effects of maintaining a healthy diet in combination with other healthy lifestyle choices across all stages of life.

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